REMARKS

Reconsideration of this application is respectfully requested in view of the following remarks.

Claims 27-31, 33-37, 40-43 and 46-53 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Ulrich '379 in view of Richardson. Claim 44 was rejected as allegedly obvious over Ulrich '379 and Richardson and Ulrich '919 in view of Richardson. Claims 32, 38, 39 and 45 were rejected as allegedly obvious over the combination of Ulrich '379, Richardson, Weithman, Bethge, Prigal and Matsuoka. Applicants respectfully traverse each of these rejections.

Richardson is cited for disclosing a sustained release formulation comprising α-lipoic acid which is based on known polymeric matrices. Richardson's preferred polymeric matrices include hydrophilic, water-swellable polymers such as hydroxymethylcellulose, hydroxypropylcellulose, etc. polyethylene oxide and porous bioerodable particles prepared from alginate and chitosan that have been lonically crosslinked. Based on this disclosure of polymeric matrices, the Examiner apparently concluded that the carriers and adjuvants used in the dihydrollpoic acid sustained release formulation disclosed in Ulrich '397, e.g. hydropropylcellulose, are chitosan equivalents. Furthermore, the Examiner alleges that a skilled person would have been motivated to include the chitosan disclosed by Richardson in the formulation of Ulrich '379 to provide a sustained release formulation with a best biocompatible matrix, since both references allegedly show similar sustained release polymers.

The Examiner has not addressed the fact that the chitosan polymer according to claim 27 has to be a cationogenic polymer to be suitable as component (a) of the sustained release formulation.

The sustained release formulation according to the present invention comprises a cationogenic chitosan polymer (a), the anionogenic α-lipoic acid component (b) and a further acid component (c). The combination and interaction of these three components (a), (b) and (c) enables a retarding adhesion of the active substance on the basis of ionic, dipolar as well as other

intermolecular interactions between the components. Fig. 1 of the specification clearly illustrates these interactions between the components of the sustained release form. To obtain the desired retarding effect it is, therefore, necessary that an interaction occurs between the cationgenic polymer component and the anionic α-lipoic acid component (b), as well as the further anionic acid component (c).

However, as is evident from the passage in the Richardson reference in col. 22, the hydrophilic water-swellable polymeric matrices described therein are clearly not cationogenic polymers. Although chitosan is in fact mentioned, it is not used as a polymeric matrix but as a starting material for the preparation of porous bioerodable particles, whereby the chitosan is ionically crosslinked with alginates. For a skilled artisan, it is, therefore, unequivocal that the ion charges of the chitosan as starting material as used to establish crosslinkages with the alginates and therefore the chitosan charges are exhausted. Thus, the polymeric particle matrices according to Richardson, which are obtained from chitosan, do not exhibit a free cationic charge and, therefore, are not able to undergo any interaction with anionogenic components of the formulation, e.g. α-lipoic acid. These interactions are, however, the basis of the sustained release form of claim 27 which provides a controlled and improved release of the α-lipoic acid.

In support, the Examiner is referred to the paragraph bridging pages 6 to 7 where it is clearly stated that the dosage form of the present invention is characterized by a combination of an anionogenic active ingredient with a cationogenic carrier matrix whereby, because of the predominantly ionic interactions between the two main components, the active ingredient is released in delayed fashion.

On page 8, lines 23 to 27, it is again stated that the mechanism of a delayed active ingredient adhesion is described and explained on the basis of ionic, dipolar and other intermolecular interactions, between the cationogenic polymer and the active ingredient with anionogenic characteristics on the one hand and the acid component on the other hand.

Page 13, lines 25 to 34, discloses that the cationogenic polymer has to interact first with an acid component which differs from the α-lipoic acid in order to ensure a sufficient hydration of the polymer. Thus, for this hydration step, it is mandatory that the polymer has a cationogenic

character. In contrast, the matrix particles according to Richardson cannot undergo sufficient hydration because they are already in a crosslinked state.

At page 14, second paragraph, it is disclosed that the cationogenic character of the polymer component of the sustained release form is required. In fact, it is demonstrated that even low concentrations of acetic acid can increase the effect of chitosan sustaining the release of the active ingredient. The acid component contributes to rendering the free primary amino groups of the cationogenic chitosan polymer more accessible to the active ingredient, this being the α-lipoic acid, since the degree of hydration of the polymer is thereby increased. Consequently, the highest release-sustaining effect of the polymer is reached as soon as the acetic acid reaches a concentration which makes all the primary amino groups of the polymer accessible to the α-lipoic acid.

Richardson, therefore, does not overcome the deficiencies of Ulrich '379.

To reiterate, the presently claimed invention provides a sustained release form which provides controlled and improved release and improved adsorption of α-lipoic acid or an α-lipoic acid derivative , leading to improved bioavailability thereof. The claimed sustained release form is based on the interaction between the cation charge of the cationogenic chitosan polymer (a) and the anion charge of the component (b) (α-lipoic aid or a derivative thereof) and the component (c) (the further acid component).

Neither, Ulrich '379 nor Richardson '190, nor a combination thereof, provide any hint or suggestion that a claimed combination of a cationogenic chitosan and an anionic acid compound can improve the release properties of a composition containing α-lipoic acid as an anionogenic active ingredient.

In view of the foregoing, allowance is respectfully requested.

Any fees necessary to enter this response or to otherwise maintain pendency of this application may be charged to deposit account no. 50-0624.

Respectfully submitted,

FULBRIGHT & JAWORSKI L.L.P.

By _____
James R. Crawford
Reg. No. 39,155

666 Fifth Avenue
New York, N.Y. 10103
(212) 318-3148